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Original Article

Role of vitamin A on retinal function in infants at risk of retinopathy of prematurity

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ABSTRACT

Background: Preventive therapy for retinopathy of prematurity (ROP) is still lacking, and visual improvements after treatment are often poor. Vitamin A or plasma concentrations of retinol are low in preterm infants and reflect reduced hepatic stores. Early intramuscular (IM) vitamin A supplementation enhances survival and improves respiratory function at 36 weeks postmenstrual age (PMA) and may also protect against ROP. This study was planned to test the hypothesis that dark adapted retinal sensitivity in preterm infants is improved by early high dose supplementation of vitamin A.
Method: A randomized double blind controlled trial of infants at risk of ROP (32 weeks gestation and or 1500 g birth weight) was performed on 76 infants, who had been admitted to neonatal units of Government Medical College, Jammu. Ocular abnormalities and predicted non-survival were excluded from the trial.
Results: 36 infants were randomly selected and kept as healthy controls, while, 40 were supplemented with the minimum 5 x IM Vitamin A injections till day 14. Plasma retinol was significantly higher in supplemented group as compared to the control group at 7^{th} day, while at 28^{th} day and at 36^{th} week PMA, this difference was not significant. Retinal sensitivity (log σ) at 36^{th} week was greater in the supplemented group, and some relation to Vitamin A intake per Kg weight of the infant over the first 4 weeks of life was found.
Conclusion: Vitamin in as IM dose to preterm infants at the risk of ROP improves retinal sensitivity at 36 week' PMA.

Keywords: Vitamin A, Plasma Concentrations of Retinol, Retinopathy of Prematurity, Post-Menstrual Age

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INTRODUCTION

Retinopathy of prematurity (ROP) is a common retinal neovascular disorder and a major cause of visual impairment or blindness in preterm infants, even in the context of current standard care.[1] Preventive therapy for ROP is still lacking,[2] and visual improvements after treatment are often poor. Retinopathy of prematurity pathogenesis is associated with the regulation of the vascular endothelial growth factor (VEGF) and insulin like growth factor (IGF-1).[3] Inhibition of VEGF at the neovascular phase may prevent destructive neovascularization[4] but VEGF as a treatment should be weighted carefully, as VEGF also promotes normal physiologic development of blood vessels in many tissues.[5]

Vitamin A is an essential micronutrient for normal visual function. Plasma concentrations of retinol are low in preterm infants and reflect reduced hepatic stores.[6] Early intramuscular (IM) vitamin A supplementation enhances survival and improves respiratory function at 36 weeks postmenstrual age (PMA) and may also protect against retinopathy of prematurity, (ROP), a disease of developing retina.[7] Body stores of vitamin A are in the liver but significant amounts are also assimilated into the eye. Retinaldehyde formed by reversible oxidation of retinol is an essential constituent of rhodopsin contained within photoreceptor membrane disc in the outer retina. The rhodopsin content of human retina increases several fold during the third trimester of pregnancy,[8] but how this process proceeds postnatally in prematurely born infants is not understood. In preterm infants, dark adapted retinal sensitivity increases greatly between 30 and 50 postmenstrual weeks in association with increasing ERG amplitude, but sensitivity remains reduced at term-corrected age compared with new born infants.[9]

Very less number of studies have measured functional ocular stores of retinol in preterm infants, therefore this study was planned to test the hypothesis that dark adapted retinal sensitivity in preterm infants is improved by early high dose supplementation of vitamin A

MATERIAL AND METHODS

A randomized double blind controlled trial of infants at risk of ROP (32 weeks gestation and or 1500 g birth weight) was performed on 76 infants, who had been admitted to neonatal units of Government Medical College, Jammu. Ocular abnormalities and predicted non-survival were excluded from the trial. All parents get informed via written informed consent and the study was duly approved by Institutional Ethical Committee. Randomization was undertaken by staff that had no contact with participant, and was stratified for gestational age. Supplemented infants received 10 000 IU vitamin A via IM injections 3 times weekly from day 2, continued until commencement of oral supplementation on day 14, or for a maximum of 12 doses. Following randomization infants details were labeled on the sealed bags and contain either an empty box or a vial of aquasol A within a similar box were delivered to the neonatal unit.

Total intake of vitamin A for each infant was calculated from fluid and drug charts using manufacturer composition tables. Mean daily intake of vitamin A (IU/Kg/d) was computed using weight at the midpoint of each week .[10] infants were observed for any toxicity like clinical assessment of skin, joints and intracranial pressure and week assessment of liver function tests. Blood for estimation of plasma retinol was collected at the time was measured f birth and repeat at 7^{th}, 28^{th} and 36 weeks PMA after 24 hours of administration of vitamin A. Samples were protected from light, frozen, and subsequently analyzed by solvent extraction and high-pressure liquid chromatography with ultraviolet detection.[11]

Relative dose response (RDR) was measured at 36 weeks PMA as an indicator of hepatic stores of vitamin A, a base line blood level was obtained and 2000 IU/Kg vitamin A was given orally prior to feed. A base line blood level was obtained and 2000 IU/Kg vitamin A was given orally prior to feed.[12] Another specimen of blood was obtained 3 hours later, and RDR was calculated as the change in plasma retinol relative to post dose plasma retinol concentration. Routine oral vitamin supplements were withheld on the day of RDR. Retinal function test was assessed at 36 weeks PMA by ERG. The primary outcome was cone corrected dark adapted, retinal sensitivity at 36 weeks PMA; associations were also sought between total vitamin A, plasma retinol levels, and RDR.

Statistical analyses were carried out using MS Excel 2010 software. 2-sample t-test was performed to ascertain the significance of the findings.

RESULTS

Out of the 138 eligible infants in the hospital, only 102 were approached, and only 76 parents consented for study and were recruited. Out of these 76, 36 were randomly selected and kept as healthy controls, while, 40 infants were supplemented with the minimum 5 x IM Vitamin A injections till day 14. Depending upon the condition of the infant, the range of IM doses of

Vitamin A administered was: 5-12. No infant showed signs of Vitamin A toxicity. The healthy controls matched the supplemented group in terms of GA, birth weight, oxygen dependency at 36 weeks' PMA, etc. 10 infants of supplemented group required ROP treatment, while 13 infants required the same in the control group. (Table 1)

Table 1: Characteristic data of Supplemented infants and Controls

	Supplemented	Control	P-value
GA (Median)	28.56	28.31	0.882
Birth Weight, gm (Median)	1239	1286	0.804
Postnatal Steroids	4 / 40 (10%)	3 / 36 (8.33%)	0.906
Assisted Ventilation	31 / 40 (77.5%)	25 / 36 (69.44)	0.224
Duration of support, Days	1.5	1.5	0.313
Oxygen dependency at 36th week'PMA	12 / 36	12 / 31	0.457
ROP, any stage	10 / 36	13 / 31	0.309
Intraventricular Hemorrhage	6 / 40	5 / 36	0.538
Death	4	5	

*P<0.05 = significant

Plasma retinol concentration at birth did not differ between the groups. 7 infants had received postnatal steroids by 28th day and and additional 3 by 36th week PMA; their plasma retinol values were higher than those of infants who did not receive post-natal steroids and were excluded from further analysis. Plasma retinol was significantly higher in supplemented group as compared to the control group at 7th day, while at 28th day and at 36th week PMA, this difference was not significant. 19% infants in supplemented group had deficient stores of RDR. Red cell DHA was not much different between the cases and controls either. (Table 2). Retinal sensitivity (log σ) at 36th week was greater in the supplemented group, and some relation to Vitamin A intake per Kg weight of the infant over the first 4 weeks of life was found. (Figure 1).

Table 2: Plasma retinol concentrations and RDR

	Supplemented		Control		
Plasma retinol (µmol/L)	n	Median (IQR)	n	Median (IQR)	P value
Day 1	40	0.5 (0.25)	36	0.5 (0.30)	>0.05
Day 7	40	1.0 (0.55)	35	0.8 (0.30)	<0.05*
Day 28	37	0.8 (0.35)	33	0.6 (0.40)	>0.05
36 Week'PMA (RDR Predose)	36	0.8 (0.30)	31	0.7 (0.20)	>0.05
RDR	36	13, range: -20 to +40	31	14, range: -21 to +46	>0.05
RDR > 10%	36	19 (52.8%)	31	17 (54.8%)	>0.05
RDR ≥ 20%	36	9 (25%)	31	8 (25.8%)	>0.05

*P<0.05 = significant

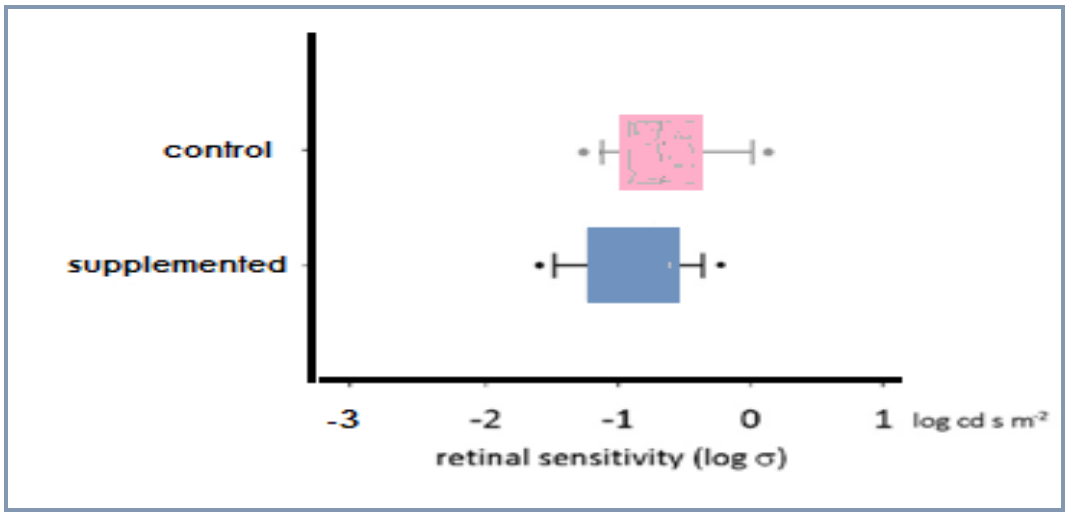

Figure 1: Distribution of retinal sensitivity values in control and supplemented groups

The correlation between retinal sensitivity and total vitamin A intake per kilogram over first 4 weeks of life, was positive, but not significant. At 36th week'PMA, retinal sensitivity did not show any significant relation with RDR or plasma retinol either.

DISCUSSION

The sensitivity of the preterm infant retina increases greatly between 30- and 40-weeks' PMA and is likely that an increase in both rod outer segment length and retinal rhodopsin content is seen. [8] Studies have shown that early high-dose vitamin A supplementation resulted in an increase in retinal sensitivity of 0.19 log unit, thus reducing by >40% the deficit in retinal sensitivity associated with extremely preterm birth.[9]

Oral vitamin A is poorly absorbed in the smallest infants,[13] and there is no single vitamin A preparation suitable for intravenous use, but there remains widespread reluctance to give IM supplementation.[14] Besides, the optimal dose of vitamin A for preterm infants has not been defined. Plasma concentrations of vitamin A do not correlate well with body stores,[15] and so functional measurement of vitamin A sufficiency is likely to be a more reliable indicator of vitamin A requirements. It is proposed that in addition to its antioxidant properties, retinal sufficiency of vitamin A allows adequate rhodopsin availability for phototransduction, thus, a role for vitamin A supplementation in the prevention of ROP is biologically plausible and consistent with the findings of this study. Tyson et al [6] and Woodruf et al.[12] have discussed that plasma retinol at 36 weeks' PMA <0.7 mmol/L in in preterm infants is indicative of reduced hepatic stores. Insignificant relation retinal sensitivity with RDR in our study may indicate that different mechanisms may control retinal accretion and hepatic storage of vitamin A in the preterm population. In the current study, we have chosen a value for increase in retinal sensitivity of 0.35 log units, based on the mean difference in retinal sensitivity at 40 weeks' PMA observed between preterm infants and term infants, as shown by Hamilton et al.[9] A deficit of 0.2 log unit deficit in retinal sensitivity at 36 weeks' PMA in infants with threshold ROP prior to treatment and a similar deficit in retinal sensitivity was reported for groups of term and preterm infants with differing red cell DHA levels.[16]

The difficulty involved in our study showed that this technique is only feasible in infants who do not require respiratory support, as most of the infants are at a risk of ROP and least likely to be fit enough to complete an ERG study at 36th week' PMA. Deferring ERG testing to 40 weeks' PMA could give a better result, but would also miss the stage of maturity at which ROP peaks in incidence and severity.

Early high-dose IM vitamin A supplementation improves retinal sensitivity at 36 weeks' PMA in preterm infants at risk of ROP. This study indicates that the beneficial effects of early vitamin A supplementation for preterm infants extend to the developing retina as well as the developing lung and, for the first time, suggests a role for early vitamin A supplementation in promoting postnatal retinal maturation.

CONCLUSION

There are beneficial effects of early Vitamin A supplementation for preterm infants, which get extended to the developing retina as well. Vitamin in as IM dose to preterm infants at the risk of ROP improves retinal sensitivity at 36 week' PMA.

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